REMARKS

Reconsideration of this application is respectfully requested.

Claims 91-149 were previously pending in this application. New claim 150 has been added above. No claims have been amended or canceled by this paper. Accordingly, claims 91-150 are presented for further examination in this application.

Commensurate with their complete and broad disclosure and prompted in part by the indication in the April 19, 2000 Office Action of allowable subject matter (objected claim 149), Applicants have added new claim 150 above. This claim is directed to an *in vivo* process for producing a specific nucleic acid. The process comprises two steps, the first step (a), providing a conjugate which is capable of producing a specific nucleic acid when present in a cell. The conjugate comprises a protein-nucleic acid construct, comprising three subelements: (i) at least one promoter; (ii) at least one segment of the specific nucleic acid comprising a sequence coding for a protein; and (iii) an RNA polymerase. The second step (b) in new claim 150 calls for introducing the conjugate into a cell, thereby producing the specific nucleic acid. Support for new claim 150 is found variously in the specification. See, for example, Figure 3 (A-C) as well as present dependent claims 143 and 145.

Before addressing the art-related rejections, Applicants would like to point out that the present application is not a provisional application. As a non-provisional application, Applicants are entitled to the priority filing date of the immediate parent application, U.S. Patent Application Serial No. 08/182,621, filed on January 13, 1994. When the parent application was revived, it was done so for purposes of continuity so that the present application could be filed as a

continuation application, thus receiving the benefit of the parent's January 13, 1994 filing date. This benefit is stated in the June 2, 1999 Decision Granting Petition (see page 2, second full paragraph " . . . Therefore, continuity between the above-identified continuation application and prior application No. 08/182,621 has been established."). A copy of the June 2, 1999 Decision Granting Petition is attached to this Amendment as Exhibit 1.

The First Rejection Under 35 U.S.C. §102

Claims 91-96 and 99-120 stand rejected under 35 U.S.C. §102(e) as anticipated by Walker, U.S. Patent No. 5,455,166, issued on October 3, 1995. In the Office Action (pages 3-5), the Examiner stated:

> Walker et al teaches an in vitro process for producing more than one copy of a specific nucleic acid, the process being independent of a requirement for the introduction of an intermediate structure for the production of the specific nucleic acid, (Abstract, Figures 1 and 2), the process comprising the steps of:
>
> (a) providing a nucleic acid sample containing or suspected of containing the sequence of the specific nucleic acid (Example 1, column 10, lines 58-63 and Example 2, column 11, line 63 and Example 3, column 12, lines 49-53);
>
> (b) contacting the sample with a mixture comprising:
>
> (i)nucleic acid precursors (Figure 1)
>
> (ii) one or more specific nucleic acid primers each of which is complementary to a distinct sequence of the specific nucleic acid (Figure 1 and Example 2, column 11, lines 56-58), and
>
> (iii) an effective amount of a nucleic acid producing catalyst (Example 1, column 11, lines 1-7); and
>
> (c) allowing the mixture to react under isostatic conditions, temperature, buffer and ionic strength, thereby producing more than one copy of the specific nucleic acid (Figures 1 and 2 and Examples I2, column 12, lines 3-6).
>
> Walker teaches the process wherein the nucleic acid is single stranded or double-stranded DNA (Figures 1 and 2 and Examples 1 and 2).

Walker teaches the process wherein the nucleic acid is in solution (Example 2, column 11, lines 56-62).

Walker teaches the process further comprising the steps of treating the specific nucleic acid with a restriction enzyme capable of producing blunt ends (Figures 1 and 2, column 8, lines 20-60 and example 1, column 11, line 5 and example 2, column 12, line 5).

Walker teaches the process wherein the nucleic acid is isolated or purified prior to the contracting step or the reacting step (Example 3, column 12, lines 49-52).

Walker teaches the process wherein the releasing step is carried out by means of a restriction enzyme (Figures 1 and 2).

Walker teaches the process wherein the nucleic acid precursors are selected from nucleoside triphosphates and nucleoside triphosphate analogs, or a combination thereof (column 8, lines 20-60 and Example 3, column 12, line 58).

Walker teaches the process wherein the nucleic acid precursors are selected from ATP, GTP, CTP, UTP, or TTP (Figures 1 and 2 and Example 2, column 12, lines 1-3).

Walker teaches the process wherein the nucleoside triphosphates analogs are naturally occurring or synthetic, or a combination thereof (Figures 1 and 2 and Example 2, column 12, lines 1-3).

Walker teaches the process wherein at least one of the nucleoside triphosphate analogs is modified on the phosphate (column 8, lines 20-60 and Example 3, column 12, line 58).

Walker teaches the process wherein the specific nucleic acid primers contains a 3'-hydroxyl group or an isosteric configuration of heteroatoms containing sulfur (Figures 1 and 2 and Example 2, column 11, lines 56-57)

Walker teaches the process wherein the specific nucleic acid primers are substantially complementary to one another and does not contain more the five complementary to base-pairs in the sequences therein (Column 15, SEQ ID Nos; 5 and 6).

Walker teaches the process wherein the specific nucleic acid producing catalyst is selected from DNA polymerase (Example 1, column 11, lines 1-5).

Walker teaches the process further comprising the step of detecting the product by means of incorporating into the product a

> labeled primer (Example 3, column 12, line 65 to column 13, line 13 and Table III).
>
> Walker teaches the process further comprising the step of regenerating the one or more specific nucleic acid primers for additional production processes (Figures 1 and 2).

The first anticipation rejection is respectfully traversed.

In response, Applicants respectfully point out that Walker's patent does not disclose a process for producing more than one copy of a specific nucleic acid that is *independent of a requirement for the introduction of an intermediate structure*, as defined in the present invention and preamble of claim 91, for example. Walker's Abstract and Figures 1 and 2 were cited in the Office Action, but in fact both figures clearly depict an intermediate structure that is formed by the introduction of a restriction enzyme site that is not normally present in the specific target nucleic acid being amplified by Walker. See the first step in Walker's Figure 1, and the second step in his Figure 2.

Thus, there is a lack of identity of material elements between the present invention and Walker's patent, namely, a copying process that is independent of a requirement for the introduction of an intermediate structure. Accordingly, the anticipation rejection cannot be reasonably maintained and its withdrawal is respectfully requested.

The Second Rejection Under 35 U.S.C. §102

Claims 142, 144, 146 and 147 stand rejected under 35 U.S.C. 102(b) as anticipated by Zaichikov et al. [Bioorganicheskaia Khimia 14(1):121-124 (1988)]. In the Office Action (page 5), the Examiner stated:

> Zaichikov et al teaches a conjugate comprising a protein-nucleic acid construct, the nucleic acid construct not coding for said protein,

> and which conjugate produces a nucleic acid when present in a cell (Abstract, lines 1-3).
>
> Zaichikov et al. teaches a conjugate wherein the protein comprises an RNA polymerase or a subunit thereof (Abstract, lines 1-6).

The second anticipation rejection is respectfully traversed.

In response, Applicants respectfully point out that Zaichikov et al. do not disclose or even suggest that their conjugate could produce a nucleic acid when present in a cell, unlike the subject matter of the claims at hand. In fact, Zaichikov et al. do not even make any mention of *in vivo* processes or applications for their disclosed conjugate. Zaichikov et al. lacks any mention of a step of introducing a conjugate into a cell for producing a specific nucleic acid as required in Applicants' claimed processes. Because Zaichikov et al. lack this material element, the anticipation rejection based on this document is untenable. Applicants respectfully request, therefore, reconsideration and withdrawal of the rejection.

The Third Rejection Under 35 U.S.C. §102

Claims 142-149 stand rejected under 35 U.S.C. 102(b) as anticipated by Knorre et al. [IZV SIB OTD AKAD NAUK SSSR SER BIOL NAUK 0(2):98-104 (1989)]. In the Office Action (page 6), the Examiner stated:

> Knorre et al. teaches an in vivo process for producing a specific nucleic acid, the process comprising a protein-nucleic acid construct, the nucleic acid construct not coding for said protein, and which conjugate produces a nucleic acid when present in a cell (Abstract, lines 1-19).
>
> Knorre et al. teaches a conjugate wherein the protein comprises an RNA polymerase or a subunit thereof (Abstract, lines 1-6) and the nucleic acid construct contains the corresponding RNA polymerase promoter (Abstract, lines 1-8).

The third anticipation rejection is respectfully traversed.

In response, Applicants respectfully point out that as in the case of Zaichikov et al. cited *supra.*, Knorre et al. likewise do not disclose or suggest that their conjugate could produce a nucleic acid when present in a cell, unlike the subject matter of the claims at hand. No mention of *in vivo* processes or applications for their disclosed conjugate is made in Knorre's document. More specifically, Knorre et al. lacks any mention of a step of introducing a conjugate into a cell for producing a specific nucleic acid as required in Applicants' claimed processes. Accordingly, the anticipation rejection based upon Knorre et al. cannot reasonably be maintained. Reconsideration and withdrawal of this anticipation rejection is respectfully requested.

Commonality of Ownership

Applicants assert that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made.

The First Rejection Under 35 U.S.C. §103

Claims 91-120 stand rejected under 35U.S.C. 103(a) as being unpatentable over Walker, U.S. Patent No. 5,455,166, issued on October 3, 1995, cited *supra.*, in view of Matthews et al. [Analytical Biochemistry 169:1-25 (1988)]. In the Office Action (pages 7-8), the Examiner stated:

> Walker teaches the processes of claims 91-96 and 99-120 as described above.
>
> Walker does not teach the isolation or purification of the specific nucleic acid by means of sandwich hybridization or capture sandwich hybridization or capture sandwich hybridization.
>
> Matthews et al teaches the isolation or purification of the specific nucleic acid by means of sandwich hybridization or capture sandwich hybridization (Figures 9, 10, 12, 13 and 14).

> It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to substitute sandwich hybridization model of Matthews et al. in the method of Walker, since Matthews et al states, "The sandwich hybridization strategy is not limited to quantitation of a nucleic acid species, but can easily be applied to detection of altered restriction sites in DNA, providing the exact mutation to be detected is known (page 16, column 1, lines 7-11)." An ordinary practitioner would have been motivated to combine the sandwich hybridization model of Matthews et al. in the method of Walker, in order to achieve the express advantages noted by Matthews et al. of a method which provides easy application to detection of altered restriction sites in DNA.

The first obviousness rejection is respectfully traversed.

As indicated above in the first anticipation rejection above, Applicants' claimed processes are distinguished from Walker's disclosure by virtue of the fact that the latter specifically requires the introduction of an intermediate structure in his cited Figures 1 and 2, cited in the Office Action and discussed *supra*. Because the primary reference, Walker, does not touch Applicants' claimed processes, the combination of Walker and Mathews et al. must also fail as a matter of logic and the law to reach Applicants' claimed invention.

Applicants respectfully request reconsideration and withdrawal of the first obviousness rejection.

The Second Rejection Under 35 U.S.C. §103

Claims 91-96 and 99-128 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Walker, U.S. Patent 5,455,166, issued on October 3, 1995, cited *supra*., in view of Romano et al., U.S. Statutory Invention Registration Number H1,825, published on December 7,1999). In the Office Action (pages 8-9), the Examiner stated:

Walker teaches the processes claims 91-96 and 99-120 as described above.

Walker does not teach primers comprising at least one ribonucleic acid segment.

Walker does not teach removing of primer-code sequences from the product by digestion with an enzyme ribonuclease H.

Romano et al teaches primers comprising at least one ribonucleic acid segment (Abstract, Table 1 and 2).

Romano et al teaches removing of primer-coded sequences from the product by digestion with an enzyme ribonuclease H (Column 6, lines 29-41)

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to substitute RNA primer based isothermal transcription and amplification model of Romano et al. in the method of Walker, since Romano et al states, "The purpose of applying such an assay would be to determine the presence and level of these transcripts, and to use these level for prognosis and/or therapeutic to combine the RNA primer based isothemal transcription and amplification model of Romano et al. in the method of Walker, in order to achieve the express advantages noted by Romano et al. of a method which provides utilization in screening of blood donors, epidemiological studies, and in clinical practice for prognosis and/or therapeutic management.

The second obviousness rejection is respectfully traversed.

In response, Applicants respectfully point out that as in the case of the primary reference, Walker et el., the secondary reference, Romano et al., also discloses a process that requires and depends upon formation of an intermediate structure. In the case of Romano et al., a non-native nucleic acid sequence (an RNA promoter) is introduced into a copy of the target nucleic acid being amplified. As such, neither Walker et al. or Romano et al., nor a combination of the two, would have rendered Applicants' present invention obvious at the time it was made.

The Third Rejection Under 35 U.S.C. §103

Claims 91-96, 99-120 and 129-136 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walker, U.S. Patent No. 5,455,166, issued on October 3,1995, cited *supra.*, in view of Gerdes et al., U.S. Patent No. 5,955,351, issued on September 21,1999. In the Office Action (pages 9-10), the Examiner stated:

> Walker teaches the processes of claims 91-96 and 99-120 as described above.
>
> Walker does not teach one or more specific chemically-modified primers each of which primer is substantially complementary to a distinct sequence of the spe cific nucleic acid.
>
> Walker does not teach removing of primer-coded sequences from the product by digestion with an enzyme ribonuclease H.
>
> Gerdes et al teaches one or more specific chemically-modified primers each of which primer is substantially complementary to a distinct sequence of the specific nucleic acid (Examples 3,4,5,6,7 and 8 and SEQ ID Nos: 1-13).
>
> Gerdes et al teaches removing of primer-coded sequences from the product by digestion with an enzyme ribonuclease H (Example 4, column 10, lines 47-56).
>
> It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to substitute the chemically-modified primer model of Gerdes et al. in the method of Walker, since Gerdes et al states, "The process according to the present invention is suitable for the determination of all nucleic acid target sequences. The sensitivity and accuracy of this process are improved compared to the processes currenty used by those skilled in the art. The invention offers the possibility of contamination free, rapid and reliable determination of the presence of specific amplified target nucleic acid (column 4, lines 41-47)." An ordinary practitioner would have beenn motivated to combine chemically-modified primer model of Gerdes et al. in the method of Walker, in order to achieve the express advantages noted by Gerdes et al. of a method which provides the possibility of contamination free, rapid and reliable determination of the presence of specific amplified target nucleic acid.

The third obviousness rejection is respectfully traversed.

As discussed earlier in this paper, the primary reference, Walker, fails to reach Applicants' present invention. See the discussion above relating to the first anticpation rejection. In the case of the secondary reference, Gerdes et al., the application for this patent was filed as Provisional Application No. 60/000,885 on July 13, 1995. Because the present invention enjoys the benefit of a January 13, 1994 filing date. See the June 2, 1999 Decision Granting Petition attached to this paper as Exhibit 1. Accordingly, Gerdes et al. cannot be relied upon as a prior art document to support the obviousness rejection at hand. Applicants respectfully request, therefore, reconsideration and withdrawal of the third obviousness rejection.

The Fourth Rejection Under 35 U.S.C. §103

Claims 91-96,99-120 and 129-141 stand rejected under U.S.C.103(a) as being unpatentable over Walker, U.S. Patent No. 5,455,166, issued on October 3, 1995, cited *supra.*, in view of Gerdes et al., U.S. Patent No. 5,955,351, issued on September 21, 1999, also cited *supra.*, further in view of Courey et al. [Journal of Molecular Biology 202:35-43 (1988)]. In the Office Action (pages 10-11), the Examiner stated:

> Walker in view of Gerdes et al. teach the processes of claims 91-96, 99-120 and 129-136 as described above.
>
> Walker in view of Gerdes et al. do not teach one or more specific unmodified primers each of which primer comprises at least one non-complementary sequence to a distinct sequence to the specific nucleic acid such that upon hybridization to the specific nucleic acid at least one loop structure is formed.
>
> Courey et al teaches one or more specific unmodified primers each of which primer comprises at least one non-complementary sequence to a distinct sequence of the specific nucleic acid such that upon hybridization to the specific nucleic acid at least one loop structure is formed (Figures 2,5 and 6).

> It would have been prima facie obvious to one having ordinary skill in the art at time the invention was made to substitute the loop forming supercoiling model Courey et al. in the method of Walker, since Walker states, "The invention further relates to methods of generating amplified products which can function as probes or templates for sequence analysis (column 4, lines 41-47)." Courey et al provides further motivation as he states, "Lengths of cruciform arms are strongly dependent on sequence imperfections in the palindrome (page 36, column 1, lines 11-14)." An ordinary practitioner would have been motivated to combine the loop forming supercoiling model of Courey et al. in the method of Walker, in order to achieve the express advantages noted by Courey et al. of a method which provides the detection of sequence imperfections in a nucleic acid sample.

The fourth obviousness rejection is respectfully requested.

At the outset, Applicants point out that Walker is deficient in at least one material element required in their present invention. As discussed above in the third obviousness rejection, Gerdes et al. was first filed as as provisional application subsequent to Applicants' January 13, 1994 priority filing date. Thus, Gerdes et al. is not prior art to the present invention and it cannot be used to supplement the deficiencies in either Walker or Courey et al. With respect to the latter, Applicants respectfully point out that Courey's disclosure regarding the effect of sequences in supercoiled DNA is irrelevant to Walker or Gerdes et al. Both Walker and Gerdes et al. describe amplicons that are linear, double-stranded pieces of DNA. No supercoiling is disclosed, formed, envisioned or even capable of forming in Walker or Gerdes et al. Thus, the proposed combination of Courey et al. with the other two documents, one of which is not prior art to Applicants' present application, is not proper. Applicants respectfully request, therefore, that the fourth obviousness rejection be withdrawn upon further reconsideration, thereby placing all of the pending claims in condition for allowance.

Allowable Subject Matter

Applicants sincerely appreciate the indication from the Examiner that claim 149 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitaitons of the base claim and any intervening claims.[1] Applicants respectfully maintain, however, that claim 142 is patentable over the cited art of record in this application. Therefore, claim 149 will remain in its present form, pending further examination in this application.

Submission of Art-Related Documents

Applicants are presently retrieving and assembling art-related documents in connection with the present application. As soon as that process has been completed and an indication that this application has been revived has been received, Applicants' attorney will submit all such documents in an Information Disclosure Statement for consideration by the Examiner.

Favorable action is respectfully requested.

* * * * * * *

[1] As indicated in the opening remarks of this paper, Applicants have added new claim 150 above, prompted in part by the indication that the subject matter of claim 149 is allowable if rewritten to incorporate all of the limitations of the base claim and any intervening claims.

SUMMARY AND CONCLUSIONS

Claims 91-150 are presented for further examination. New claim 150 has been added above.

The fee for adding new independent claim 150 is $40. The Patent and Trademark Office is hereby authorized to charge the amount of $40 to Deposit Account No. 05-1135. No other fee or fees are believed due in connection with this Amendment. In the event that any other fee or fees are due, however, The Patent and Trademark Office is hereby authorized to charge the amount of any such fee(s) to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully submitted,

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